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Comparative haemodynamic dose response effects of propranolol and labetalol in coronary heart disease

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SUMMARY The immediate haemodynamic dose response effects of beta blockade (propranolol: 2 to 16 mg) were compared with those of combined alpha beta blockade (labetalol: 10 to 80 mg) in a randomised study of 20 patients with stable angina pectoris. After control measurements, the circulatory changes induced by four logarithmically cumulative intravenous boluses of each drug in equivalent beta blocking doses were evaluated at rest, after which comparison of the effects of the maximum cumulative dose of each was undertaken during a four minute period of supine bicycle exercise.

Propranolol, at rest, induced significant dose related reductions in heart rate and cardiac output, with reciprocal increases in the systemic vascular resistance and pulmonary artery occluded pressure; systemic arterial pressure was unchanged. Labetalol was followed by significant dose related decreases in systemic blood pressure and vascular resistance associated with a significant increase in cardiac output; heart rate and pulmonary artery occluded pressure were unchanged. The slope of the left ventricular pumping function curve relating output to filling pressure from rest to exercise was significantly depressed by propranolol but unchanged after labetalol.

The less deleterious effects on left ventricular haemodynamic performance after alpha beta blockade in contrast to beta blockade alone in ischaemic heart disease may be attributable to the concomitant reduction in left ventricular afterload associated with the alpha blocking activity of labetalol.

A major consequence of coronary heart disease is a reduction in left ventricular haemodynamic performance; the increased workload of exercise frequently results in its acute but reversible pumping failure.[1–3] The symptomatic effectiveness of beta blocking drugs is a result of the reduction in heart rate and myocardial contractility, two of the major determinants of left ventricular oxygen consumption.[4 5] These haemodynamic advantages, however, may be offset to a varying extent by the accompanying increase in end-diastolic pressure[6 7] and volume[8 9] which result from blockade of the inotropic beta adrenoceptors in the left ventricle. Increase in end-diastolic pressure can be expected to increase subendocardial coronary resistance, and the increase in end-diastolic volume to offset some of the saving in left ventricular oxygen consumption achieved by the reduction in heart rate and myocardial contractility.

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A further disadvantage of beta blocking drugs in coronary heart disease is their propensity to increase the peripheral vascular resistance; this stems from two sources. First, the decrease in systemic arterial pressure[10] and the increase in left atrial pressure[7] can be expected to result in stimulation of arterial baroreceptors and intra-atrial stretch receptors, respectively, and thus reflexly augment the already increased peripheral vascular resistance.[11] Second, beta blocking drugs may directly increase the peripheral vascular resistance by blockade of the vasodilator beta-2 adrenoceptors in striated muscle; this may also apply even to "cardioselective" drugs in the doses usually used clinically.[7] Left ventricular dysfunction in patients with coronary heart disease is aggravated by any increase in aortic impedance.[12 13] Thus, the vasoconstriction induced either directly or indirectly by beta blocking drugs can be expected to aggravate the primary impairment of left ventricular pumping function in these patients. As these disadvantages originate from an increase in left ventricular afterload,

theoretically they could be countered by a concomitant reduction in aortic impedance induced by peripheral vasodilatation. The following study was undertaken to contrast the alpha beta properties of labetalol[14] with propranolol to test this hypothesis that combined alpha beta blockade would be haemodynamically more advantageous in patients with stable coronary heart disease than beta blockade alone.

Patients and methods

PATIENTS (Table 1)

Twenty male patients, aged 35 to 64 years, with exercise-induced angina and electrocardiographic and angiographic evidence of severe but clinically stable coronary heart disease were studied. All were normotensive and in sinus rhythm and none had clinical or radiographic signs of left ventricular failure. There were no contraindications to beta blockade in any patient. Patients were well matched for age (propranolol 52±3 (35 to 64); labetalol 49±2 (38 to 59); the duration of angina was somewhat longer in patients on labetalol (3·2±0·5 years) compared with those randomised to propranolol (2·6±0·4 years). Eleven of the 20 had a history of previous myocardial infarction six to 60 months before the study: six in the propranolol (three anterior infarction) and five (four anterior) infarction) in the labetalol group. The distribution of pathological involvement of the coronary arteries was similar. Left ventricular angiography showed dyskinesia in seven of the patients randomised to propranolol (>one site involved in all) and in eight of those randomised to labetalol (>one site involved in five); none had aneurysms. Angiographic ejection fraction at rest was similar in both groups.

Short acting nitrates were the only prescribed drugs in the 72 hours before the study and no intercurrent medication was necessary in the 12 hours before any investigation. Informed consent was given by all patients and the procedure was agreed by the hospital Ethics Committee.

DESIGN OF INVESTIGATION (Fig. 1)

The study was designed as an open, between group comparison with patients randomised before the haemodynamic studies to treatment either with propranolol or labetalol. Patients were familiarised with the exercise technique beforehand and the bicycle workload which each could sustain for four minutes without distress was determined. In each patient the control study started with a four minute period of supine bicycle exercise at their predetermined symptom limiting load (25 to 50 W); haemodynamic measurements were made during the fourth minute of the exercise period. When the circulation had restabilised, usually after 10 to 15 minutes, the resting studies were undertaken. Measurements were made during eight successive four minute periods. Haemodynamic variables were recorded during the last two minutes of each of the first four periods after injection of 10 ml saline into the pulmonary artery. After this either propranolol 2, 2, 4, and 8 mg (cumulative dose 2, 4, 8, and 16 mg) or labetalol 10, 10, 20, and 40 mg (cumulative dose 10, 20, 40, and 80 mg) were similarly injected and resting measurements repeated during the

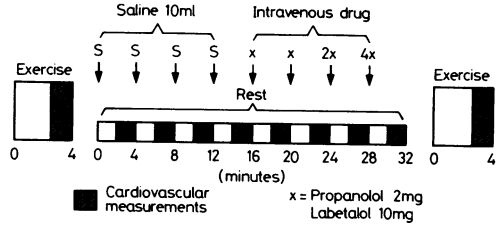

Fig. 1 *Study design.*

Table 1 *Summary of angiographic and haemodynamic findings in patients studied*

Drug	*Left ventricular angiography*					*Coronary angiography*			*Haemodynamic profile*			
	Normal	*Dyskinesia*			*Ejection fraction*	*Vessels involved*			*Rest*		*Exercise*	
		*Ant**	*Inf*	*Ap*		*1*	*2*	*3*	*PAOP†* (*mmHg*)	*CO‡* (*l/min per m²*)	*PAOP* (*mmHg*)	*CO* (*l/min per m²*)
Propranolol (n=10)	3	6	5	4	44±4 (23–58)§	1	5	4	12 ± 1	3·6 ±0·2	21 ± 2	6·1 ±0·4
Labetalol (n=10)	2	6	3	4	38±6 (28–65)	2	4	4	12 ± 2	3·0 ±0·2	25 ± 5	4·4 ±0·3

Data presented as mean±SEM.
*Ant, anterior; Inf, inferior; Ap, apical.
†PAOP, pulmonary artery occluded pressure.
‡CO, cardiac output.
§(Range).

third and fourth minutes after each injection. Patients were then immediately re-exercised for four minutes at the same bicycle workload as previously and measurements again made during the fourth minute of the exercise period. Venous blood samples for the measurement of plasma drug concentrations were taken at the time of the resting haemodynamic measurements, four minutes after each intravenous dose. The doses of propranolol and labetalol were chosen for two reasons. They encompass dose ranges often used in clinical situations, and the ratio of beta blocking activity in man between propranolol and labetalol is approximately 1:5 by weight.[15]

LABORATORY TECHNIQUES, MEASUREMENTS, AND STATISTICS

Heart rate was measured from the electrocardiogram and systemic arterial pressure through a brachial artery catheter. Pulmonary vascular pressures were measured through a balloon-tipped thermodilution catheter positioned radiographically so that inflation of the balloon resulted in replacement of the pulmonary artery pressure record by a typical pulmonary wedge tracing (pulmonary artery occluded pressure). Pressures were externally transduced with strain gauges and recorded together with heart rate on an ultraviolet recorder. Zero reference point for transduced pressures was mid-chest in the vertical plane of the sternal angle. Mean pressures were integrated electronically and heart rate and pressures were averaged over two respiratory cycles. Cardiac output was measured in triplicate by thermodilution and automatically computed (Instrumentation Laboratories 601 Computer/602 Recorder). A gas operated constant speed injector (OMP Model 3700) was used with 10 ml dextrose saline at 0°C as indicator. This system is linear in vitro, with a coefficient of variance of 6% in patients at rest and 7% during steady bicycle exercise. Systemic vascular resistance was calculated by conventional means. Left ventricular ejection fraction was calculated from the planimetric measurement of the systolic and end-diastolic frames of the cineangiogram in the right anterior oblique projection.

The plasma concentration of both drugs was measured using high performance liquid chromatography with fluorimetric detection. The assay for propranolol was specific for unchanged drug, linear over the range 10 to 1000 ng/ml (coefficient of variation 7·2%) and with a lower limit of sensitivity of 2·5 ng/ml.[16] The assay for labetalol was specific, linear over the plasma concentration range 50 to 2500 ng/ml (coefficient of variation: 5%) and with a lower limit of sensitivity of 2 ng/ml.

The probability of statistical significance of differences between control and post-drug data was tested by analysis of variance of repeated measurements.[17] Tukey's multiple comparison procedure[18] was used to generate the single value for two confidence levels, thus allowing the significance of differences between the incremental effects of each drug on each haemodynamic variable, both at rest and during exercise, to be ascertained.

Results

The study was accomplished without untoward incident in any patient. Eight of the 10 patients given propranolol and seven of those given labetalol volunteered the information that the severity of the exercise-induced anginal pain was less after the drug than in the control study.

HOMOGENEITY OF GROUPS (Table 1)

The randomisation achieved comparable distribution between the groups in terms of the extent of the angiographic coronary artery disease. The duration of symptoms was marginally longer in the labetalol group but their overall left ventricular performance, in terms of the relation between filling pressure and output during exercise was substantially more depressed than that of patients randomised to propranolol.

MEASUREMENTS IN CONTROL STUDIES AT REST

In the control study the variability of the haemodynamic variables at rest was small in both groups and none showed any significant trend to change over the 16 minute period of measurement. For the purposes of analysis the measurements for each group from the four control periods were therefore averaged. In the resting control period the average coefficients of variation (range) for the 20 patients were: systolic blood pressure 1·7% (0·3 to 2·8%), diastolic blood pressure 2% (1·2 to 4·0%), heart rate 3·3% (0 to 6·2%), cardiac output 3·3% (1·7 to 5·9%), and pulmonary artery occluded pressure 8% (3·5 to 12·3%).

HAEMODYNAMIC EFFECTS OF PROPRANOLOL (Fig. 2 and 3; Tables 2 and 3)

At rest

After the cumulative doses of propranolol there was no change in systolic, diastolic, or mean systemic arterial pressure compared with control measurements. There were, however, progressive reductions in heart rate and cardiac output and significant increases in the pulmonary artery occluded pressure and in the systemic vascular resistance.

During exercise

After the cumulative dose of 16 mg propranolol the systolic arterial pressure was reduced ($p<0·01$) without

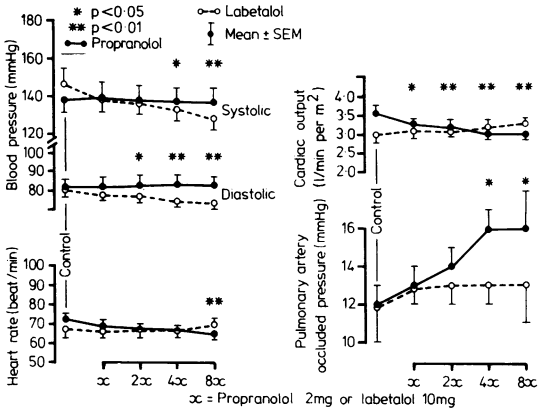

Fig. 2 *Comparative haemodynamic dose response effects of propranolol and labetalol in 20 patients with coronary heart disease. Statistics related to comparison of incremental changes induced by both drugs at each of the four increasing doses.*

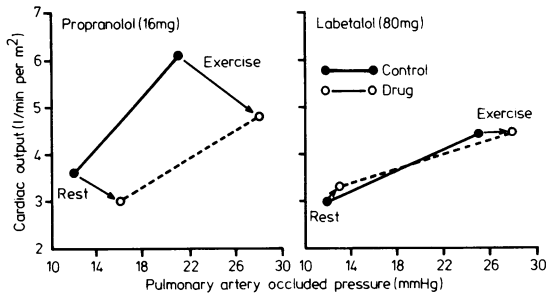

Fig. 3 *Comparison of the functional relation between left ventricular filling pressure and cardiac output, at rest and during exercise, after a cumulative dose of propranolol (16 mg) or labetalol (80 mg).*

change in the diastolic or mean pressure. Heart rate and cardiac output were both reduced ($p<0·01$) and the systemic vascular resistance was increased ($p<0·01$). The pulmonary artery occluded pressure increased by an average of 7 mmHg ($p<0·01$).

HAEMODYNAMIC EFFECTS OF LABETALOL (Fig. 2 and 3; Tables 2 and 3)

At rest

After the cumulative doses of labetalol there were statistically significant progressive reductions in systolic, diastolic, mean systemic arterial pressure, and systemic vascular resistance. there was a progressive increase in cardiac output but no significant trend of change in either heart rate or pulmonary artery occluded pressure.

During exercise

After the cumulative dose of 80 mg labetalol there were significant reductions in systolic, diastolic, and mean systemic arterial pressure ($p<0·01$), heart rate ($p<0·01$), and systemic vascular resistance ($p<0·05$) without change in the cardiac output. The pulmonary artery occluded pressure increased by an average of 3 mmHg ($p<0·05$).

Table 2 *Haemodynamic dose response effects of intravenous propranolol and labetalol at rest in 20 patients with severe coronary heart disease*

Variable	*Drug*	*Control*	*Cumulative intravenous dose*				*Value between drugs determining significance†*	
			×	2×	4×	8×	*p<0·05*	*p<0·01*
Systolic blood pressure (mmHg)	Propranolol	139±7	140±7	139±7	138±7	138±7		
	Labetalol	147±8	139±7 **	138±6 **	134±6 **	129±6 **	11·03	15·1
Diastolic blood pressure (mmHg)	Propranolol	82±4	83±4	83±5	84±4	83±4		
	Labetalol	81±4	78±3 **	77±3 **	75±3 **	73±3 **	4·5	6·0
Mean blood pressure (mmHg)	Propranolol	103±6	104±5	104±5	104±5	104±6		
	Labetalol	107±5	102±5 **	101±4 **	97±4 **	94±4 **	6·4	8·8
Heart rate (bt/min)	Propranolol	73±2	69±2 **	67±2 **	66±2 **	64±2 **		
	Labetalol	67±4	66±3	66±3	66±3	69±3	7·3	10·0
Cardiac output (l/min per m²)	Propranolol	3·6±0·2	3·3±0·1 **	3·2±0·2 **	3·0±0·1 **	3·0±0·1 **		
	Labetalol	3·0±0·2	3·1±0·2	3·1±0·1	3·2±0·2 *	3·3±0·1 **	0·3	0·4
Pulmonary artery occluded pressure (mmHg)	Propranolol	12±1	13±1	14±1 **	16±1 **	16±2 **		
	Labetalol	12±2	13±1	13±1	13±1	13±2	2·3	3·2
Systemic vascular resistance (dyne cm^{-5} s^{-1}/m^2)	Propranolol	2379±193	2592±200*	2685±236**	2787±192**	2868±230**		
	Labetalol	2948±208	2679±161**	2616±108**	2477±119**	2338±105**	320	440

Data presented as mean ± SEM.
×, propranolol 2 mg or labetalol 10 mg.
Probability of significant difference from control *p<0·05
**p<0·01.
†Value for comparison of changes from control induced by the drugs at any cumulative dosage.

Table 3 *Haemodynamic effects at rest and during supine bicycle exercise after the maximum cumulative doses of propranolol (16 mg) and labetalol (80 mg)*

Variable	*Drug*	*Rest*		*Exercise*	
		Control	*Drug*	*Control*	*Drug*
Systolic blood pressure (mmHg)	Propranolol	139±7	138±7	170±7	156±7**
	Labetalol	147±8	129±6**	166±9	151±9**
Diastolic blood pressure (mmHg)	Propranolol	82±4	83±4	93±4	93±4
	Labetalol	81±4	73±3**	89±5	83±4**
Mean blood pressure (mmHg)	Propranolol	103±6	104±6	119±5	117±6
	Labetalol	107±5	94±4**	119±7	111±6**
Heart rate (bt/min)	Propranolol	73±2	64±2**	100±4	88±3**
	Labetalol	67±4	69±3	87±4	83±3**
Cardiac output (l/min/m^2)	Propranolol	3·6±0·2	3·0±0·1**	6·1±0·4	4·8±0·3**
	Labetalol	3·0±0·2	3·3±0·1*	4·4±0·3	4·5±0·3
Pulmonary artery occluded pressure (mmHg)	Propranolol	12±1	16±2**	21±2	28±2**
	Labetalol	12±2	13±2	25±5	28±4*
Systemic vascular resistance (dyne cm^{-5} s^{-1}/m^2)	Propranolol	2379±193	2868±230**	1616±103	2024±143**
	Labetalol	2948±208	2338±105**	2353±287	2088±186*

Data presented as mean±SEM.
Drug, propranolol 16 mg or labetalol 80 mg.
Probability of significant difference from control *p<0·05 **p<0·01.

Table 4 *Comparison of changes induced by equivalent beta blocking doses of propranolol and labetalol in 20 patients with coronary heart disease*

Variable	*Drug*	*Cumulative intravenous dose*			
		×	2×	4×	8×
Systolic blood pressure (mmHg)	Propranolol	+ 1	0	− 2	− 1
	Labetalol	− 7	− 9	− 13*	− 17**
Diastolic blood pressure (mmHg)	Propranolol	+ 1	+ 1	+ 2	+ 2
	Labetalol	− 4	− 5	− 7**	− 9**
Mean blood pressure (mmHg)	Propranolol	+ 1	+ 1	+ 1	+ 1
	Labetalol	− 5	− 6*	− 10**	− 13**
Heart rate (bt/min)	Propranolol	− 4	− 6	− 7	− 8
	Labetalol	− 1	− 1	− 1	+ 2**
Cardiac output (l/min per/m^2)	Propranolol	− 0·3	− 0·4	− 0·5	− 0·6
	Labetalol	+ 0·1*	+ 0·1**	+ 0·2**	+ 0·3**
Pulmonary artery occluded pressure (mmHg)	Propranolol	+ 2	+ 3	+ 4	+ 5
	Labetalol	+ 1	+ 1	+ 1*	+ 1*
Systemic vascular resistance (dyne cm^{-5} s^{-1}/m^2)	Propranolol	+213	+306	+408	+489
	Labetalol	−269**	−333**	−471**	−610**

Data presented as difference from control. ×, propranolol 2 mg or labetalol 10 mg.
Statistics relate to between drug comparison at each dose level *p<0·05; **p<0·01.

COMPARISON OF HAEMODYNAMIC CHANGES INDUCED BY LOGARITHMICALLY CUMULATIVE DOSES OF PROPRANOLOL AND LABETALOL AT REST (Table 4)

Labetalol induced a linear dose related decrease in systemic arterial pressure at rest; there was no change after propranolol. The heart rate decrease after the two drugs was similar except that the highest dose of propranolol resulted in a greater decrease in heart rate than labetalol (p<0·01). Propranolol induced a significantly greater reduction in cardiac output than labetalol at all doses. There were directionally similar increases in pulmonary artery occluded pressure in both groups, but the increase was significantly greater after propranolol at the two highest doses. Propranolol increased and labetalol decreased the calculated systemic vascular resistance at all doses (p<0·01).

COMPARISON OF EFFECTS OF PROPRANOLOL AND LABETALOL ON LEFT VENTRICULAR PUMPING FUNCTION (Fig. 3)

The effects of propranolol and labetalol on the relation between the cardiac output and pulmonary artery occluded pressure at rest and during exercise showed distinct differences. Propranolol was followed by a significant shift to the right in the rest-to-exercise relation between left ventricular filling pressure and its pumped output (p<0·01); increase in filling pressure and reduction in output both contributed to this changed relation. Labetalol induced no substantial

change in the relation between these two variables despite the initially greater overall depression of left ventricular function.

PLASMA CONCENTRATIONS

The plasma concentrations (mean±SEM) after the four cumulative intravenous boluses of propranolol were 77±30, 92±20, 191±55, and 454±118 ng/ml. The respective mean plasma concentrations of labetalol were 319±07, 420±142, 826±249, and 1125±209 ng/ml. The plasma concentrations showed significant log-linear increases after each drug (propranolol $r=0\cdot78$, $p<0\cdot001$; labetalol $r=0\cdot82$, $p<0\cdot001$).

Discussion

Beta blocking drugs have long been used in the symptomatic treatment of angina pectoris[10 19] and in the attempt to abort post-myocardial infarction arrhythmias.[20] More recently they have been advocated for secondary prevention of coronary heart disease, both orally[21 22] and by the intravenous route.[23 24] For the physiological and pharmacodynamic reasons already stated, however, blockade of beta adrenoceptors alone in patients with severe coronary heart disease has potential haemodynamic disadvantages. Some of these were clearly shown in our study. Propranolol was associated with a significant increase in systemic vascular resistance and left ventricular filling pressure, reflecting a substantial increase in the indices determining left ventricular afterload.[5] In contrast, labetalol was not associated with any further deterioration in left ventricular pumping performance despite considerably greater impairment at the outset. As both drugs have equivalent cardiac beta blocking activity in the 5:1 ratio of the doses used in our study[15] and as both are non-cardioselective, the most likely cause of this striking difference in their haemodynamic activity is the vasodilatation induced by labetalol.

After propranolol, the log linear increase in plasma concentration achieved (77 to 454 ng/ml) was well within the therapeutic range; antianginal activity of propranolol is present between 30 to 90 ng/ml,[25] and antihypertensive activity appears at plasma concentrations in excess of 120 ng/ml.[26] Equally the log linear increase in plasma concentration of labetalol (319 to 1125 ng/ml) exceeded that necessary to attain an equivalent degree of cardiac beta blockade (that is 150 ng/ml[27]). At these plasma concentration ranges the immediate haemodynamic effects of the two drugs were in sharp contrast both at rest and during dynamic exercise. At rest propranolol resulted in a dose related depression of cardiac pumping activity; the increase in systemic vascular resistance was presumably both reflex in origin (from the increase in left atrial pressure[28]) and also the result of direct blockade of vasodilator beta-2 adrenoceptors in the peripheral arteriolar resistance vessels. In contrast, labetalol resulted in a dose related increase in the pumped output of the left ventricle at the same filling pressure and heart rate, presumably because of the reduction in left ventricular afterload consequent upon its direct vasodilator activity. During exercise the separation of the haemodynamic effects of the two drugs was even greater, despite the greater initial impairment of left ventricular performance in the labetalol group. In the latter group the relation between the filling pressure of the left ventricle and its output was largely unchanged by combined alpha and beta blockade whereas this haemodynamic relation was significantly depressed after propranolol. Again, presumably as a reflection of further depression of left ventricular function, the systemic vascular resistance during exercise was increased after propranolol but unchanged after labetalol. Thus, the contrasting pharmacodynamic effects of the two drugs in these patients with coronary heart disease were largely explicable by the possession of vasodilator alpha adrenoceptor blocking activity by labetalol.

These results with propranolol are in accord with previous single dose[29 30] and multiple dose response studies[31] in patients with coronary heart disease. The circulatory effects of labetalol in normal volunteers,[15] and in patients with essential hypertension,[32] were similar to those we recorded in our patients. The only other haemodynamic evaluation of labetalol in normotensive patients with angina pectoris was a single dose study carried out at rest.[33] Ten minutes after an average intravenous bolus of 1·5 mg/kg systemic blood pressure and vascular resistance were reduced to a similar order to that after the maximum cumulative dose in the present study, cardiac output was unchanged and there was a small insignificant fall in pulmonary wedge pressure. These results are compatible with ours and highlight the important influence of dose response studies and physiological exercise in analysing the haemodynamic effects of a drug.

How far these results can be extrapolated to the medical treatment of patients with angina cannot be decided from these studies. Labetalol, however, has been shown to be symptomatically effective, both in normotensive (unpublished observations) and hypertensive patients with angina pectoris.[34 35] Our results also suggest that the drug may be particularly useful in the treatment of angina patients with severe left ventricular dysfunction or in those with an inadequate response to beta blocking drugs alone.

It is important, however, to emphasise that these observations, however haemodynamically instructive, were based on the results of intravenous studies, and

can be extended to the wider therapeutic field only with caution. Definitive studies of the clinical efficacy of combined alpha and beta blockade during long term treatment of patients with angina pectoris and those with asymptomatic coronary heart disease undergoing secondary preventive treatment are necessary before the true therapeutic value of this new pharmacological approach can be decided. Our results, however, furnish an optimistic basis for the institution of such studies in patients with stable coronary heart disease.

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